

SUPPLEMENTAL MATERIAL

The supplemental material contains the following:

1. **Supplementary Table 1:** Hemostatic characteristics across genotypes of replicated SNPs
2. **Supplementary Table 2:** Loci with suggestive association findings in the GWAS of epinephrine-mediated platelet aggregation in African Americans
3. **Supplementary Table 3:** Loci with suggestive association findings in the GWAS of collagen-mediated platelet aggregation in African Americans
4. **Supplementary Table 4:** ADP-mediated Platelet Aggregation across Genotypes of the Two Novel Genetic Variants
5. **Supplementary Table 5:** Loci with suggestive association findings in the GWAS of ADP 2 μ M-mediated platelet aggregation in African Americans
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Supplementary Table 1: Hemostatic characteristics across genotypes of replicated SNPs

rs12041331				
Genotypes	AA (N=110)	GA (N=367)	GG (N=348)	P-value*
Platelet Count ($10^9/L$)	277.8 (72.8)	274.2 (70.8)	264.4 (66.0)	0.07
Mean Platelet Volume ($10^{-15}/L$)	7.7 (0.84)	8.0 (0.90)	8.0 (0.87)	0.06
Fibrinogen (mg/dL)	428.6 (142.1)	422.4 (122.3)	406.2 (127.8)	0.34
Collagen-induced Platelet Aggregation (%)	44.2 (35.2)	62.7 (30.9)	69.2 (26.1)	2.74×10^{-11}
Epinephrine-induced Platelet Aggregation (%)	27.3 (33.3)	46.0 (35.0)	62.0 (33.8)	2.82×10^{-12}
ADP(2 μ M)-induced Platelet Aggregation (%)	30.7 (25.6)	37.4 (27.8)	47.1 (28.2)	5.8×10^{-9}
ADP(10 μ M)-induced Platelet Aggregation (%)	69.1 (19.5)	74.4 (18.7)	80.4 (14.7)	3.2×10^{-10}
rs11202221				
Genotypes	GG (N=3)	TG (N=114)	TT (N=706)	P-value*
Platelet Count ($10^9/L$)	245.0 (72.5)	274.3 (64.7)	269.9 (69.9)	0.86
Mean Platelet Volume ($10^{-15}/L$)	7.7 (0.83)	7.8 (0.95)	7.9 (0.88)	0.41
Fibrinogen (mg/dL)	359.5 (157.7)	414.7 (131.1)	416.4 (127.1)	0.30
Collagen-induced Platelet Aggregation (%)	55.3 (44.5)	55.8 (32.2)	64.2 (30.2)	0.09
Epinephrine-induced Platelet Aggregation (%)	18.7 (6.5)	41.8 (34.1)	51.9 (36.4)	0.12
ADP(2 μ M)-induced Platelet Aggregation (%)	28.7 (11.0)	29.5 (23.1)	42.6 (28.8)	4.8×10^{-8}
ADP(10 μ M)-induced Platelet Aggregation (%)	67.3 (24.0)	71.5 (21.7)	77.0 (16.9)	0.01
rs6566765				
Genotypes	CC (N=297)	CT (N=403)	TT (N=125)	P-value*
Platelet Count ($10^9/L$)	265.9 (62.8)	272.9 (70.1)	274.0 (80.0)	0.44
Mean Platelet Volume ($10^{-15}/L$)	8.0 (0.88)	7.9 (0.86)	7.9 (0.98)	0.95
Fibrinogen (mg/dL)	414.1 (131.9)	414.9 (124.5)	426.4 (127.5)	0.62
Collagen-induced Platelet Aggregation (%)	59.0 (33.1)	65.1 (28.6)	65.7 (30.1)	0.05
Epinephrine-induced Platelet Aggregation (%)	45.8 (37.1)	51.1 (35.8)	57.9 (33.8)	0.15
ADP(2 μ M)-induced Platelet Aggregation (%)	37.0 (28.2)	41.8 (28.4)	45.0 (27.3)	0.03
ADP(10 μ M)-induced Platelet Aggregation (%)	72.8 (19.0)	76.9 (17.5)	82.0 (12.9)	3.59×10^{-8}

Abbreviations: SNP = single nucleotide polymorphism; ADP = adenosine diphosphate

*Data is represented as mean and standard deviation. P-values for collagen and epinephrine-induced platelet aggregation are from dichotomized phenotypes using logistic models, other P-values are from linear regression. All tests were adjusted for familial correlation.

Supplementary Table 2: Loci with suggestive association findings in the GWAS of epinephrine-mediated platelet aggregation in African Americans

			GeneSTAR			PGAP			GeneSTAR (EA)		
SNP	Position	Gene	β (SE)	P-value	MAF	β (SE)	P-value	MAF	β (SE)	P-value	MAF
rs10803355_T	1:15327779	C1orf126	-0.63 (0.13)	3.43×10^{-6}	26.0%	0.11 (0.05)	0.03	30.4%	-0.07 (0.12)	0.26	29.9%
rs922987_G	2:217119491		-0.52 (0.11)	1.28×10^{-6}	41.7%	-0.07(0.05)	0.19	33.3%	-0.09 (0.09)	0.29	49.8%
rs7000642_C	8:64591068		-0.53 (0.11)	1.30×10^{-6}	40.6%	0.001 (0.05)	0.98	41.6%	-0.003 (0.10)	0.49	65.9%
rs12313736_A	12:26275226	SSPN	0.63 (0.13)	2.77×10^{-6}	17.7%	-0.07 (0.06)	0.29	22.7%	-0.001(0.23)	0.50	4.9%
rs12708769_T	16:9077749		-0.51 (0.11)	3.60×10^{-6}	28.1%	0.07 (0.06)	0.20	37.4%	-0.06 (0.10)	0.53	27.0%
rs9889955_G	17:69072972	SDK2	-0.67 (0.13)	7.54×10^{-7}	24.0%	0.07 (0.06)	0.25	25.8%	0.11 (0.11)	0.30	19.2%

Abbreviations: SNP = single nucleotide polymorphism; β = regression coefficient; SE = standard error; GeneSTAR = Genetic Study of Atherosclerosis; PGAP = Platelet Gene and Physiology; MAF = minor allele frequency; ADP = adenosine diphosphate

Note: In PGAP the epinephrine concentration of 1.5 μ M was used.

Supplementary Table 3: Loci with suggestive association findings in the GWAS of collagen-mediated platelet aggregation in African Americans

			GeneSTAR (AA)			PGAP			GeneSTAR (EA)		
SNP	Position	Gene	β (SE)	P-value	MAF	β (SE)	P-value	MAF	β (SE)	P-value	MAF
rs1766285_T	1:77160219	ST6GALNAC5	-0.58 (0.12)	1.04×10^{-6}	28.5%	0.004 (0.63)	0.99	28.8%	0.13 (0.10)	0.17	31.2%
rs16992175_C	4:36043106		-0.820(0.15)	1.04×10^{-7}	10.9%	-1.01 (1.01)	0.31	8.6%	-0.33 (0.40)	0.28	7.3%
rs7728135_A	5:67134354		-0.76 (0.15)	8.98×10^{-7}	18.0%	0.21 (0.71)	0.76	17.7%	-0.03 (0.13)	0.39	23.7%
rs6951019_T	7:673749	PRKAR1B	-0.87 (0.19)	3.07×10^{-6}	10.4%	2.24 (0.84)	7.8×10^{-3}	13.1%	1.08 (1.05)	0.24	8.3%
rs4590481_C	8:72877955		-0.67 (0.14)	1.38×10^{-6}	45.0%	0.21 (0.57)	0.71	48.5%	-0.09 (0.14)	0.32	21.4%
rs2387916_T	15:91068340	LOC388177	-0.78 (0.16)	1.68×10^{-6}	15.4%	-0.26 (0.87)	0.76	14.1%	0.04 (0.09)	0.35	50.6%

Abbreviations: SNP = single nucleotide polymorphism; β = regression coefficient; SE = standard error; GeneSTAR = Genetic Study of Atherosclerosis; PGAP = Platelet Gene and Physiology; MAF = minor allele frequency; AA = African Americans; EA = European Americans

Note: In PGAP the collagen concentration of 2.5 μ g/mL was used.

Supplementary Table 4: ADP-mediated Platelet Aggregation across Genotypes of the Two Novel Genetic Variants.

Genotypes		N	Allele Dose*	ADP 2 μ M (%)	ADP 10 μ M (%)
rs6566765	rs11202221				
T/T	T/T	109	0	46.6	81.6
T/T	T/G	15	1	43.5	78.2
C/T	T/T	347			
T/T	G/G	1	2	37.0	73.0
C/T	T/G	54			
C/C	T/T	250			
C/T	G/G	1	3	27.9	69.0
C/C	T/G	45			
C/C	G/G	1	4	28	41
P-value for trend				4.55×10^{-6}	4.58×10^{-9}

* Allele dose was calculated by the number of alleles associated with decreased platelet aggregation; C-allele for rs6566765 and G-allele for rs11202221.

Supplementary Table 5: Loci with suggestive association findings in the GWAS of ADP 2 μ M-mediated platelet aggregation in African Americans

			GeneSTAR (AA)			PGAP			GeneSTAR (EA)		
SNP	Position	Gene	β (SE)	P-value	MAF	β (SE)	P-value	MAF	β (SE)	P-value	MAF
rs2760480_T	1:58975709		-7.10 (1.36)	2.73×10^{-7}	44.8%	3.70 (2.67)	0.10	49.6%	-1.61 (1.32)	0.23	41.8%
rs11487952_C	1:74968400	CRYZ	6.39 (1.37)	4.22×10^{-6}	47.7%	-2.40 (2.30)	0.30	37.3%	-	-	-
rs12066611_C	1:96548296		9.73 (1.98)	1.13×10^{-6}	9.4%	3.01 (3.33)	0.37	15.0%	-	-	-
rs1446877_A	2:23069767		-8.01 (1.53)	2.49×10^{-7}	42.7%	-1.27 (2.21)	0.56	36.4%	-1.06 (1.40)	0.45	80.3%
rs4252027_C	2:113607229	IL1RN	-11.67 (2.40)	1.57×10^{-6}	6.4%	0.04 (4.89)	0.99	6.4%			
rs4683235_T	3:46476935	LTF	-9.35 (1.74)	1.30×10^{-7}	19.8%	-2.73 (3.11)	0.38	14.8%	-3.30 (2.09)	0.11	8.3%
rs13072722	3:115907655	ZBTB20	6.72 (1.41)	2.54×10^{-6}	39.1%	-3.36 (2.56)	0.20	35.5%			
rs6847949_A	4:153368734		-7.47 (1.52)	1.20×10^{-6}	26.0%	-1.60 (2.68)	0.55	18.2%	-1.56 (1.47)	0.29	22.6%
rs3846872_G	6:37172645		-7.85 (1.66)	3.06×10^{-6}	18.8%	3.63 (2.62)	0.16	26.4%	-	-	-
rs16875446_C	8:108062827		-9.52 (2.04)	3.93×10^{-6}	11.5%	-0.03 (3.24)	0.99	13.2%	-	-	-
rs12220754_A	10:2870121		11.80 (2.32)	5.46×10^{-7}	5.2%	2.32 (4.58)	0.61	6.8%	-0.94 (1.81)	0.60	13.3%
rs4934272_T	10:88567074	BMPR1A	-11.06 (2.15)	3.96×10^{-7}	10.4%	-16.39 (3.8)	1.46×10^{-5}	9.7%	-	-	-
rs7095025_T	10:88569340	BMPR1A	-11.10 (2.16)	3.66×10^{-7}	10.4%	-16.39 (3.8)	1.46×10^{-5}	9.7%	-0.02 (1.38)	0.99	75.3%
rs4934275_C	10:88607372	BMPR1A	-12.85 (2.39)	1.19×10^{-7}	9.4%	-16.01 (3.6)	7.52×10^{-5}	9.1%	0.08 (1.75)	0.96	85.4%

rs11202232_G	10:88612333	BMPR1A	-12.85 (2.39)	1.19×10^{-7}	9.4%	-17.75 (4.1)	1.26×10^{-5}	8.1%	0.08 (1.75)	0.96	85.4%
rs10887666_T	10:88649027	BMPR1A	-12.85 (2.39)	1.19×10^{-7}	9.4%	-16.92 (4.3)	9.13×10^{-5}	7.2%	0.08 (1.75)	0.96	85.4%
rs2686332_A	12:24283633	SOX5	-9.77 (2.11)	4.54×10^{-6}	11.5%	1.85 (4.37)	0.67	6.8%	-0.36 (1.29)	0.78	28.5%
rs10492301_C	12:67180245		10.36 (2.02)	4.24×10^{-7}	9.4%	-3.82 (3.31)	0.25	13.1%	1.45 (1.12)	0.20	34.5%
rs28408948_G	15:79785446		10.39 (2.23)	4.21×10^{-6}	17.0%	0.47 (3.31)	0.89	18.1%	-	-	-
rs4782624_G	16:83022667	ATP2C2	7.805 (1.66)	3.31×10^{-6}	24.0%	-3.33 (2.34)	0.15	31.8%	0.63 (2.78)	0.82	7.5%
rs12604055_T	17:29122399	ACCN1	-12.16 (2.53)	2.01×10^{-6}	5.2%	3.95 (4.26)	0.35	7.7%	-1.62 (2.10)	0.44	7.9%
rs9912932_A	17:78220928	RAB40B	-8.62 (1.84)	3.48×10^{-6}	12.5%	1.16 (2.96)	0.69	18.2%	-1.23 (1.23)	0.31	32.1%

Abbreviations: SNP = single nucleotide polymorphism; β = regression coefficient; SE = standard error; GeneSTAR = Genetic Study of Atherosclerosis; PGAP = Platelet Gene and Physiology; MAF = minor allele frequency; ADP = adenosine diphosphate; AA = African Americans; EA = European Americans

Note: In PGAP the ADP concentration of 4 μ M was used.

Supplementary Table 6: Loci with suggestive association findings in the GWAS of ADP 10μM-mediated platelet aggregation in African Americans

			GeneSTAR (AA)			PGAP			GeneSTAR (EA)		
SNP	Position	Gene	β(SE)	P-value	MAF	β(SE)	P-value	MAF	β(SE)	P-value	MAF
rs17039923_C	2:50211959	NRXN1	4.79 (0.96)	9.43×10^{-7}	24.0%	-2.70 (2.53)	0.29	25.8%			
rs7638187_T	3:3152835	TRNT1	6.19 (1.30)	2.53×10^{-6}	8.3%	1.53 (3.72)	0.68	8.9%	0.95 (0.79)	0.15	16.8%
rs1076425_C	3:52800502	ITIH1	4.96 (1.00)	1.01×10^{-6}	28.1%	-3.96 (2.96)	0.18	22.9%	0.62 (0.65)	0.28	36.5%
rs6778453_T	3:113653472		6.46 (1.38)	3.60×10^{-6}	5.2%	-7.35 (4.72)	0.12	6.4%	-1.43 (1.47)	0.33	7.4%
rs3792293_G	3:168935198	PDCD10	-4.45 (0.91)	1.34×10^{-6}	48.9%	0.06 (2.19)	0.98	41.9%	0.16 (0.62)	0.79	26.6%
rs1895742_C	4:110206737	COL25A1	4.58 (0.91)	4.29×10^{-6}	13.5%	-6.73 (3.19)	0.04	12.7%	-0.11 (0.73)	0.87	28.7%
rs6877160_G	5:178157153		4.50 (0.96)	3.73×10^{-6}	18.8%	3.91 (2.47)	0.11	24.2%	-0.14 (0.68)	0.84	30.9%
rs17636617_A	6:37609640		6.53 (1.35)	1.88×10^{-6}	5.2%	-2.47 (4.51)	0.58	5.9%	1.15 (1.16)	0.32	8.3%
rs2076473_C	6:56114802	COL21A1	4.42 (0.93)	2.54×10^{-6}	25.0%	-2.29 (2.51)	0.36	27.1%	0.57 (0.59)	0.33	57.5%
rs2791829_C	6:102399942	GRIK2	-5.93 (1.15)	3.72×10^{-7}	13.5%	-1.66 (3.55)	0.64	11.9%	-	-	-
rs2049924_T	6:113858994		4.52 (0.89)	4.94×10^{-7}	26.0%	-0.45 (2.59)	0.86	21.2%	-1.32 (0.72)	0.07	37.5%
rs750693_C	9:37723925	FRMPD1	5.32 (1.12)	2.76×10^{-6}	10.4%	-1.68 (3.75)	0.65	10.2%	1.75 (0.71)	0.01	29.1%
rs1591958_A	10:82052641		4.26 (0.86)	1.15×10^{-6}	38.5%	2.21 (2.48)	0.37	33.2%	0.91 (0.71)	0.20	18.9%
rs16928081_T	11:2277542		5.32 (1.13)	3.44×10^{-6}	13.5%	4.00 (3.89)	0.30	8.9%			
rs1506525_G	11:32001522		4.45 (0.92)	1.61×10^{-6}	24.0%	-1.46 (2.34)	0.53	34.3%	-0.21 (1.23)	0.87	17.5%

rs17755728_C	11:78691521		4.51 (0.97)	4.38×10^{-6}	11.5%	3.07 (2.86)	0.28	19.1%	0.52 (0.85)	0.54	15.9%
rs6491870_C	13:103993236		4.77 (0.99)	2.03×10^{-6}	36.5%	2.23 (2.20)	0.31	41.9%	0.62 (0.69)	0.37	28.8%
rs160475_G	14:58205393		4.83 (1.02)	2.95×10^{-6}	24.0%	2.17 (2.56)	0.40	31.8%	-1.00 (0.97)	0.37	10.9%
rs371125_G	15:56460289		6.78 (1.36)	9.28×10^{-7}	10.4%	1.33 (4.37)	0.76	7.6%			
rs244401_A	17:50675059		6.75 (1.45)	3.89×10^{-6}	7.3%	5.08 (4.89)	0.30	5.9%	-0.48 (0.72)	0.51	19.2%
rs12159423_G	22:20903637	IGL locus	4.71 (0.96)	1.23×10^{-6}	24.0%	4.25 (2.95)	0.15	18.2%	0.60 (1.11)	0.58	7.5%

Abbreviations: SNP = single nucleotide polymorphism; β = regression coefficient; SE = standard error; GeneSTAR = Genetic Study of Atherosclerosis; PGAP = Platelet Gene and Physiology; MAF = minor allele frequency; ADP = adenosine diphosphate; AA = African Americans; EA = European Americans

Note: In PGAP an ADP concentration of 4 μ M was used.

Supplementary Table 7: Loci with suggestive association findings in the GWAS of arachidonic acid-mediated platelet aggregation in African Americans

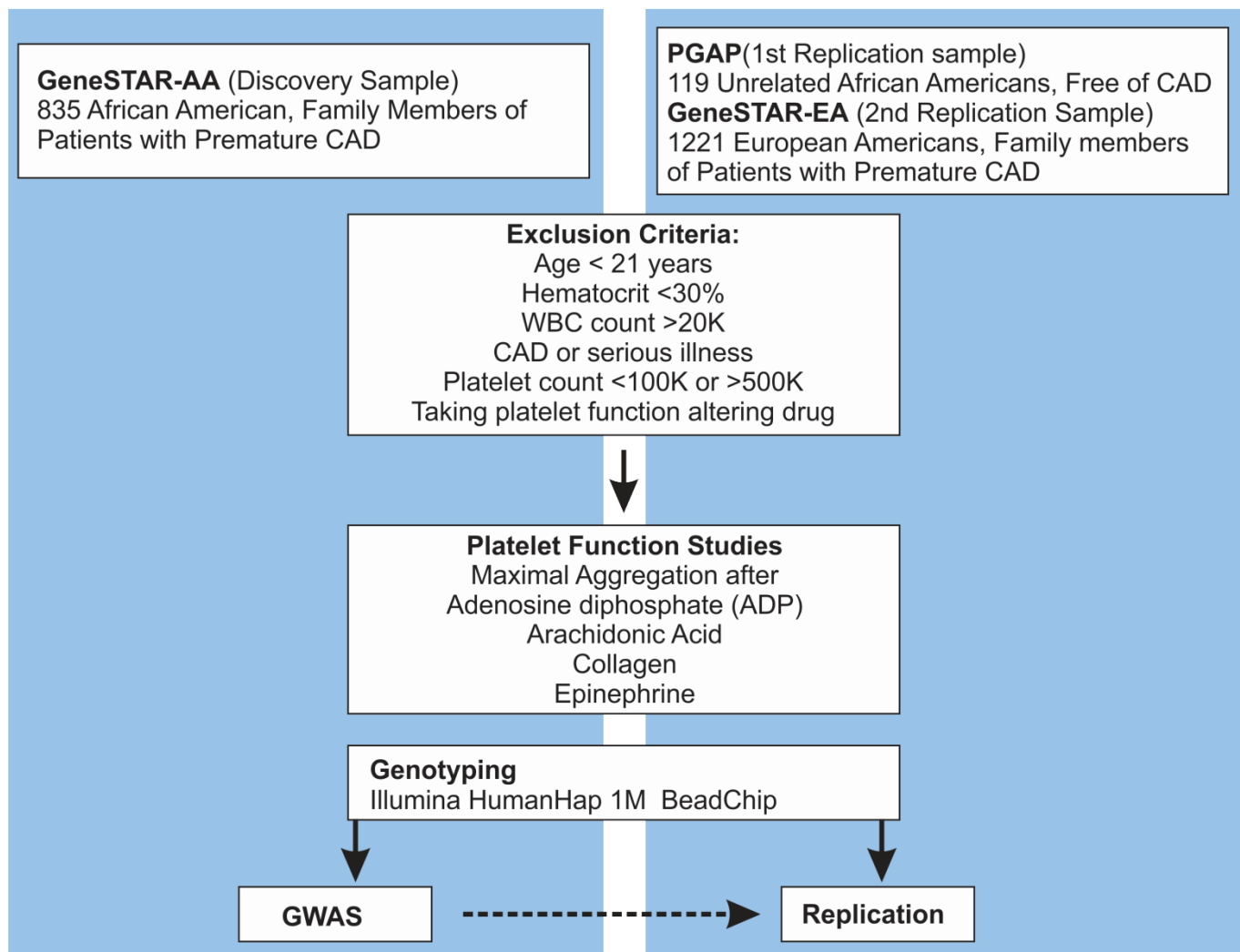
			GeneSTAR (AA)			PGAP			GeneSTAR (EA)		
SNP	Position	Gene	β (SE)	P-value	MAF	β (SE)	P-value	MAF	β (SE)	P-value	MAF
rs10921542_C	1:192591090		-3.10 (0.69)	1.12×10^{-6}	9.4%	8.17 (8.21)	0.32	6.5%	-0.52 (0.80)	0.51	9.0%
rs10204598_A	2:38205473	Near CYP1B1-AS1	3.08 (0.61)	7.65×10^{-7}	15.5%	-2.04 (5.34)	0.70	18.7%	-1.09 (0.59)	0.06	12.2%
rs11745148_T	5:12234811		-3.11 (0.63)	1.39×10^{-6}	17.2%	6.72 (4.98)	0.18	19.6%	0.72 (0.41)	0.08	34.3%
rs6554742_A	5:12714704		2.82 (0.54)	3.06×10^{-7}	27.7%	5.33 (4.27)	0.21	29.9%	-0.11 (0.52)	0.82	14.3%
rs2055437_T	5:81998598		-2.39 (0.49)	1.91×10^{-6}	31.1%	5.10 (4.61)	0.28	30.8%	0.65 (0.68)	0.34	22.8%
rs4720990_G	7:11488680	THSD7A	-2.37 (0.51)	4.71×10^{-6}	31.2%	-0.75 (4.21)	0.86	34.1%	-0.02 (0.39)	0.96	35.9%
rs10949695_C	7:157553706	PTPRN2	3.09 (0.66)	3.69×10^{-6}	15.4%	6.92 (5.39)	0.20	18.6%	-0.67 (0.44)	0.13	25.7%
rs7322119_A	13:85383398		2.48 (0.52)	2.85×10^{-6}	25.2%	1.62 (4.28)	0.70	29.2%	0.93 (0.61)	0.13	14.8%
rs948799_T	18:70004052	Near TIMM21	2.87 (0.60)	2.89×10^{-6}	19.3%	-1.79 (4.93)	0.72	17.8%	-	-	-
rs3787563_T	20:352916	RBCK1	-2.36 (0.51)	4.91×10^{-6}	52.7%	4.01 (4.03)	0.31	48.1%	0.08 (0.42)	0.84	32.6%

Abbreviations: SNP = single nucleotide polymorphism; β = regression coefficient; SE = standard error; GeneSTAR = Genetic Study of Atherosclerosis; PGAP = Platelet Gene and Physiology; MAF = minor allele frequency; AA = African Americans; EA = European Americans

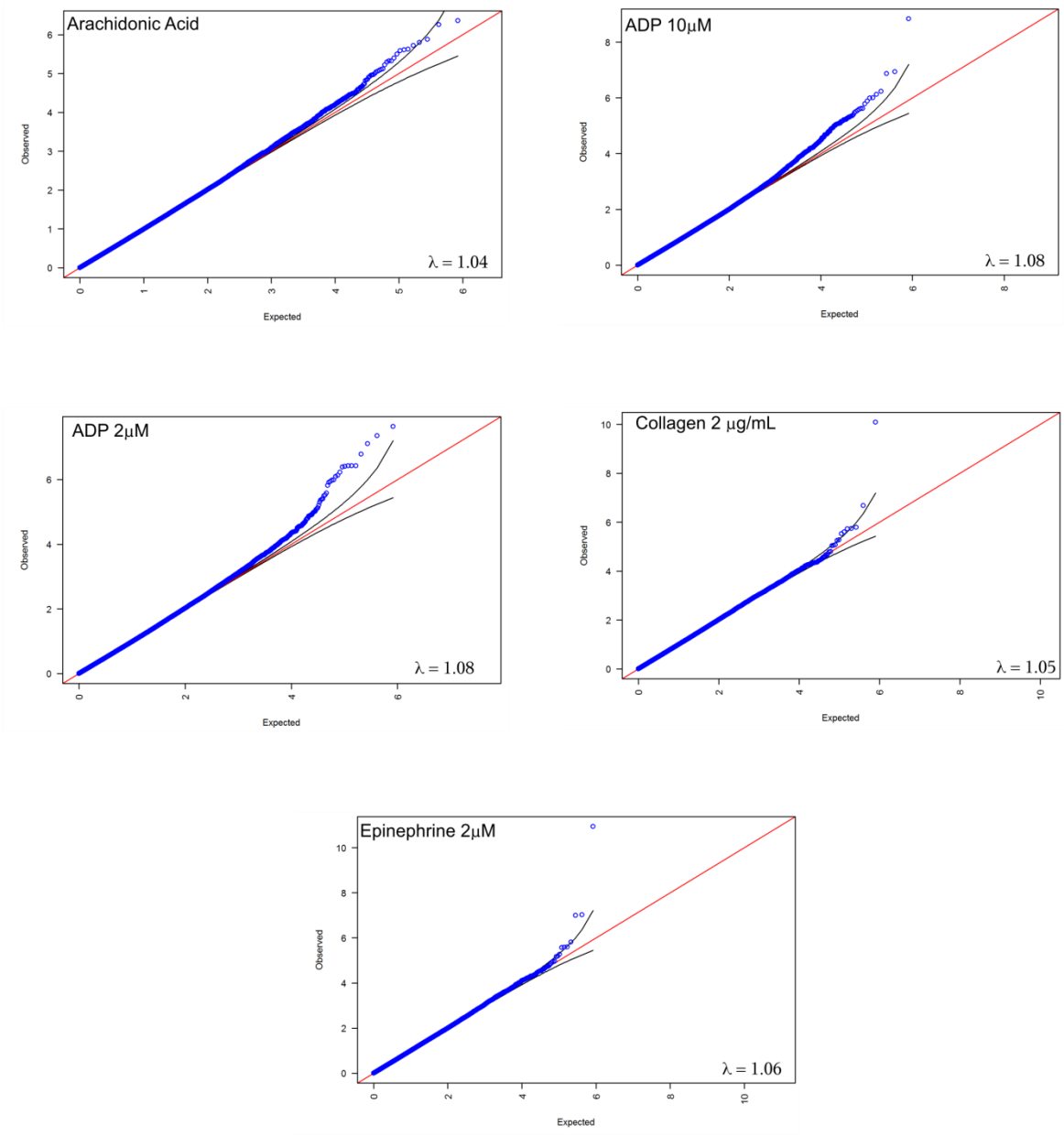
Note: In PGAP the arachidonic acid concentration of 0.5 mM was used.

Supplemental Figure 1: Study Design of the Genetic Study of Aspirin Responsiveness (GeneSTAR) and Platelet Genetics and Physiology (PGAP)

Abbreviations: GeneSTAR-AA= African American cohort of the GeneSTAR study; GeneSTAR-EA = European American cohort of the GeneSTAR study; CAD = coronary artery disease; WBC = white blood count; GWAS = genome-wide association study

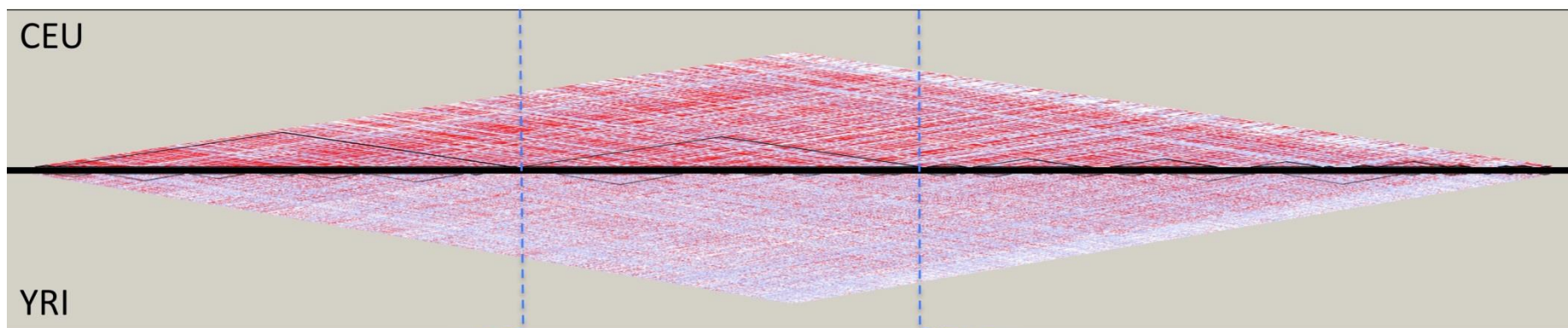


Supplementary Figure 2: Quantile-Quantile (QQ) plots with genomic inflation factors (λ)



Supplemental Figure 3: Linkage disequilibrium plots of European descent population (CEU) and African descent population (YRI) based on the data from 1000 Genomes Project

Top Panel: LD structure in a 200kb region centered on rs1120221 in the low coverage sequence data from the Thousand Genomes Project reveals extensive LD in the CEU compared to the YRI populations. **Bottom panel:** Zoomed in region of a 53 kb LD block that includes rs1120221 (yellow arrow) with an MAF of 20% in the CEU data. In contrast the MAF at rs1120221 in the YRI is only 4% and as shown by the yellow arrow, it does not fall into any LD blocks in the YRI data.



Chr10:88551472..88604569

